Remarks

This Amendment is being filed concurrently with a Request for Continued Examination. In order to advance prosecution of the Application, presented below are arguments in response to the rejections made in the final Office Action mailed on April 2, 2008.

After entry of this Amendment, claims 106-110, 112-115, 118, and 120-138, as amended, will be pending for the Examiner's review and consideration. Claims 111, 116, 117, and 119 have been canceled without prejudice. The right to pursue any or all of the subject matter of canceled claims 111, 116, 117, and 119 in this or in a subsequent continuation, continuation-in-part, or divisional application is hereby expressly reserved.

Claim Amendments:

Claim 106 has been amended to recite "one or more antioxidants." This amendment is supported, for example, on page 19, lines 1-4 of the specification as filed.

Claim 106 has also been amended to recite a method for transporting a non-steroidal anti-inflammatory drug through "intact" human or animal skin or mucous membranes. This amendment is supported, for example, on page 7, lines 7-11 of the specification as filed.

Claim 106 has also been amended to recite "wherein the vesicle is capable of penetrating through a permeability barrier having at least one constriction, and the vesicle is larger than the constriction by more than a factor of 2 and less than a factor of 4." This amendment is supported, for example, on page 1, lines 3-8 and on page 10, lines 24-26 of the specification as filed.

Claim 118 has been amended to depend from claim 106, rather than from claim 116.

Claims 124-138 have been added. Illustrative support for new claims 124-138 is summarized in the following table.

Claim	Support in Specification
124	Page 7, lines 7-11; page 26, line 1 to page 27, line 3; page 18, lines 9-12;

Claim	Support in Specification
	page 13, line 8 to page 14, line 21; page 19, lines 1-4; page 1, lines 3-8; page 10, lines 24-26
125	Page 7, lines 7-11; page 26, line 1 to page 27, line 3; page 18, lines 9-12; page 13, line 8 to page 14, line 21; page 19, lines 1-4; page 1, lines 3-8; page 10, lines 24-26; page 24, lines 6-18
126	Page 7, lines 7-11; page 26, line 1 to page 27, line 3; page 18, lines 9-12; page 13, line 8 to page 14, line 21; page 19, lines 1-4; page 1, lines 3-8; page 10, lines 24-26; page 24, lines 6-18
127	Page 7, lines 7-11; page 26, line 1 to page 27, line 3; page 18, lines 9-12; page 13, line 8 to page 14, line 21; page 19, lines 1-4; page 1, lines 3-8; page 10, lines 24-26; page 24, lines 6-18
128	Page 7, lines 7-11; page 26, line 1 to page 27, line 3; page 18, lines 9-12; page 13, line 8 to page 14, line 21; page 19, lines 1-4; page 1, lines 3-8; page 10, lines 24-26
129	Page 7, lines 7-11; page 26, line 1 to page 27, line 3; page 18, lines 9-12; page 13, line 8 to page 14, line 21; page 19, lines 1-4; page 1, lines 3-8; page 10, lines 24-26
130	Page 7, lines 7-11; page 26, line 1 to page 27, line 3; page 18, lines 9-12; page 13, line 8 to page 14, line 21; page 19, lines 1-4; page 1, lines 3-8; page 10, lines 24-26
131	Page 7, lines 7-11; page 26, line 1 to page 27, line 3; page 18, lines 9-12; page 13, line 8 to page 14, line 21; page 19, lines 1-4; page 1, lines 3-8; page 10, lines 24-26
132	Page 7, lines 7-11; page 26, line 1 to page 27, line 3; page 18, lines 9-12; page 13, line 8 to page 14, line 21; page 19, lines 1-4; page 1, lines 3-8; page 10, lines 24-26
133	Page 7, lines 7-11; page 26, line 1 to page 27, line 3; page 18, lines 9-12; page 13, line 8 to page 14, line 21; page 19, lines 1-4; page 1, lines 3-8; page

Claim	Support in Specification
	10, lines 24-26
134	Page 7, lines 7-11; page 26, line 1 to page 27, line 3; page 18, lines 9-12; page 13, line 8 to page 14, line 21; page 19, lines 1-4; page 1, lines 3-8; page 10, lines 24-26
135	Page 7, lines 7-11; page 26, line 1 to page 27, line 3; page 18, lines 9-12; page 13, line 8 to page 14, line 21; page 19, lines 1-4; page 1, lines 3-8; page 10, lines 24-26
136	Page 7, lines 7-11; page 26, line 1 to page 27, line 3; page 18, lines 9-12; page 13, line 8 to page 14, line 21; page 19, lines 1-4; page 1, lines 3-8; page 10, lines 24-26
137	Page 7, lines 7-11; page 26, line 1 to page 27, line 3; page 18, lines 9-12; page 13, line 8 to page 14, line 21; page 19, lines 1-4; page 1, lines 3-8; page 10, lines 24-26; page 10, lines 1-3
138	Page 7, lines 7-11; page 26, line 1 to page 27, line 3; page 18, lines 9-12; page 13, line 8 to page 14, line 21; page 19, lines 1-4; page 1, lines 3-8; page 10, lines 24-26; page 10, lines 1-3

Claim Rejections – 35 U.S.C. § 112:

Claims 116-118 stand rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite because, according to the Office, the recitation of "vesicle further consists essentially of one or more consistency modifiers . . ." in claim 116 is inconsistent with the recitation of "consisting essentially of" in claim 106, from which claim 116 depends. Claims 117-118 are likewise rejected because they depend from claim 116. This rejection has been rendered moot by the cancellation of claims 116 and 117 without prejudice and the amendment of claim 118 to depend from claim 106, rather than claim 116. It should be respectfully pointed out that new claim 124 recites, *inter alia*, a vesicle consisting essentially of: i) one or more phosphatidyl cholines; ii) a salt of one or more non-steroidal anti-inflammatory drugs; iii) one or more antioxidants; and iv) one or more

consistency modifiers and/or one or more stabilizers. Accordingly, it is respectfully requested that this ground of rejection be withdrawn.

Claim Rejections – 35 U.S.C. § 103(a):

Claims 106-110, 112-118 and 120-123 stand rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Vyas, et al., *J. Microencapsulation*, 1995, 12(2), 149-154 ("Vyas"); U.S. patent No. 5,585,109 to Hayward, et al. ("Hayward"); or U.S. patent No. 4,937,254 to Sheffield, et al. ("Sheffield") in combination with U.S. patent No. 5,043,165 to Radhakrishnan ("Radhakrishnan") or U.S. patent No. 5,498,420 to Edgar, et al. ("Edgar"), by themselves or together in further combination with U.S. patent No. 4,897,269 to Mezei ("Mezei"). These rejections have been rendered moot as to claims 116 and 117 by their cancellation without prejudice. As to the remaining claims, these rejections are respectfully traversed for the reasons set forth below.

Claims 106-110, 112-115, 118, and 120-123, as amended, recite, *inter alia*, methods for transporting a non-steroidal anti-inflammatory drug ("NSAID") through human or animal skin or mucous membranes, comprising administering to the skin or a mucous membrane of a human or an animal a vesicular composition comprising a vesicle that consists essentially of, *inter alia*, a salt of one or more NSAIDs and one or more antioxidants, wherein the vesicle is capable of penetrating through a permeability barrier having at least one constriction, and the vesicle is larger than the constriction by more than a factor of 2 and less than a factor of 4.

Vyas alone or in combination with Radhakrishnan, Edgar and/or Mezei:

Vyas does not disclose or suggest the recited vesicles of present claims 106-110, 112-115, 118, and 120-123, which consist essentially of: (i) one or more phosphatidyl cholines; (ii) a salt of one or more NSAIDs; and (iii) one or more antioxidants, wherein the vesicle is capable of penetrating through a permeability barrier having at least one constriction, and the vesicle is larger than the constriction by more than a factor of 2 and less than a factor of 4.

In particular, Vyas at least does not disclose or suggest either the recited antioxidant or the recited vesicle that is capable of penetrating through a permeability barrier having at least one constriction, wherein the vesicle is larger than the constriction by more than a factor of 2 and less than a factor of 4.

In addition, it is believed that Vyas teaches away from the recited vesicle. Vyas shows that vesicles having a mixture of phosphatidyl chloline and either dicetyl phosphate or cholesterol, when loaded with diclofenac, release approximately 1.7 to 3 times more diclofenac than vesicles having phosphatidyl chloline alone. *See* Vyas, p. 151, Tables 1 and 2. The vesicles of the methods of claims 106-110, 112-115, 118, and 120-123 consist essentially of (i) one or more phosphatidyl cholines, (ii) a salt of one or more NSAIDs, and (iii) one or more antioxidants, and, accordingly, do not comprise dicetylphophate or cholesterol. In view of this data, it is believed that Vyas would have discouraged one of ordinary skill in the art from preparing a vesicle consisting essentially of phophatidyl choline, without the additive dicetyl phosphate or cholesterol.

A reference that teaches away can defeat a finding of obviousness. *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1349-1350 (Fed. Cir. 2000).

None of the secondary references cited by the Office, either alone or in combination, remedies the above-described deficiencies of Vyas. Radhakrishnan does not disclose a vesicle having the recited antioxidant. Further, none of Radhakrishnan, Edgar, and Mezei discloses the recited vesicle that is capable of penetrating through a permeability barrier having at least one constriction, wherein the vesicle is larger than the constriction by more than a factor of 2 and less than a factor of 4.

Hayward alone or in combination with Radhakrishnan, Edgar and/or Mezei:

Hayward does not disclose or suggest the recited vesicles of present claims 106-110, 112-115, 118, and 120-123.

Hayward discloses "liposomal dispersions containing ***un-neutralized*** salicylic acid." Hayward, col. 1, ll. 13-15 (emphasis added). Accordingly, Hayward teaches away from using a salt of one or more NSAIDs by emphasizing the importance of using free

salicylic acid as compared with neutralized salicylic acid (*i.e.*, salicylic acid in salt form) as follows:

> • "The present invention relates to a cosmetic dispersion that allows for the incorporation of large amounts of salicyclic acid within the hydrophobic compartment of the liposomal bilayer ***without the necessity of pre-neutralization or salt formation of the corresponding salicylate*** . . ." *Id.* at col. 1, ll. 15-20 (emphasis added);
>
> • "The advantages of the [Hayward] invention include the fact that the cosmetic composition has the unexpected ability to sustain a neutral pH (7.0) in the external aqueous milieu, ***without neutralizing the salicylic acid to the corresponding salicylate***." *Id.* at col. 4, ll. 27-31 (emphasis added); and
>
> • "The formation of salts of salicylic acid, such as sodium salicylate formed by the combination of salicylic acid and sodium hydroxide, greatly improves the water solubility of the free acid, but ***substantially modifies the biological response*** to salicylic acid." *Id.* at col. 4, ll. 27-31 (emphasis added).

The Office contends that the above argument is unpersuasive because it is unclear whether salicylic acid would be in salt form in the pH range of 3 to 12 recited in present claim 108. Office Action, p. 6. It is respectfully submitted that the pK_a of salicylic acid is 2.97, and, therefore, that salicylic acid will be in its salt form throughout the pH range of 3 to 12 recited in present claim 108. *See, e.g.*, U.S. Patent No. 4,720,384, col. 6, ll. 9-10 (published January 19, 1988) (a copy of which is enclosed herewith as "Attachment A" for the Office's convenience). U.S. Patent No. 4,720,384 is also cited in a Supplemental Information Disclosure Statement, which is being filed along with this Amendment.

The Office also contends that the argument is unpersuasive because it is unclear whether all of the other NSAIDs encompassed by the claims would be in salt form in the pH range of 3 to 12 recited in present claim 108. Office Action, p. 6. In response, it is respectfully submitted that claim 108 expressly recites "a salt of one or more non-

steroidal anti-inflammatory drugs," and, accordingly, claim 106 relates to only those NSAIDs that are capable of existing in salt form at the recited pH range of 3 to 12.

None of the secondary references cited by the Office, either alone or in combination, remedies the above-described deficiency of Hayward because none of Radhakrishnan, Edgar, and Mezei discloses a vesicle having the recited salt of one or more NSAIDs.

Sheffield alone or in combination with Radhakrishnan, Edgar and/or Mezei:

Sheffield does not disclose or suggest the recited vesicles of present claims 106-110, 112-115, 118, and 120-123.

In particular, Sheffield at least does not disclose or suggest a vesicle that is capable of penetrating through a permeability barrier having at least one constriction, wherein the vesicle is larger than the constriction by more than a factor of 2 and less than a factor of 4. Rather, Sheffield teaches away from such penetration through a permeability barrier in the skin by emphasizing the delivery of the disclosed liposomes to a "site of surgical trauma" on the skin (*i.e.*, portions of the skin that have been injured, for example, by incision). Sheffield, col. 3, ll. 39-56, ll. 15-17, 42-44. When liposomes are applied to such sites of surgical trauma, it is respectfully submitted that it would not be necessary for the liposomes to penetrate any permeability barrier in the skin because such permeability barrier would already have been breached by the trauma. Sheffield does not disclose any use of the liposomes on intact skin.

None of the secondary references cited by the Office, either alone or in combination, can remedy the above-described deficiency of Sheffield because none of Radhakrishnan, Edgar, and Mezei discloses a method for transporting a NSAID through intact human or animal skin or mucous membranes, comprising administering to the skin or a mucous membrane of a human or an animal a vesicular composition comprising a vesicle that is capable of penetrating through a permeability barrier having at least one constriction, wherein the vesicle is larger than the constriction by more than a factor of 2 and less than a factor of 4.

Because none of the primary references Vyas, Hayward, or Sheffield, either alone or in combination with Radhakrishnan or Edgar by themselves or in further combination with Mezei discloses or suggests all of the recitations of present claims 106-110, 112-118 and 120-123, it is believed that the Office has failed to make out a *prima facie* case of obviousness of these claims. Accordingly, the rejections of claims 106-110, 112-118 and 120-123 under 35 U.S.C. § 103(a) as obvious over Vyas, Hayward, or Sheffield in view of Radhakrishnan or Edgar, by themselves or in further combination with Mezei cannot stand and should be withdrawn by the Office.

Conclusion:

In view of the foregoing amendments and remarks, it is respectfully submitted that the claims are in condition for allowance. Early and favorable action by the Examiner is earnestly solicited. If any outstanding issues remain, the Examiner is invited to contact the undersigned at (212) 497-7731 to discuss the same.

No fee is believed to be due for the submission of this response. Should any fees be required, please charge all such fees to Wilson, Sonsini, Goodrich & Rosati Deposit Account No. 23-2415 (Docket No. 35946-701.831).

Respectfully submitted,

Dated: August 18, 2008

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